IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIOGEN INTERNATIONAL GMBH and BIOGEN MA INC.,	)	
Plaintiffs,	)	Civil Action No. 17-823-MN (Cons.)
v.	)	
AMNEAL PHARMACEUTICALS LLC, et al.	)	
Defendants.	)	

DEFENDANTS' POST-TRIAL BRIEF

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TABLE OF ABBREVIATIONS

Term	Definition
’514 patent	U.S. Patent No. 8,399,514 (DTX1)
bid	Twice daily dosing
Biogen	Plaintiffs Biogen International GmbH and Biogen MA, Inc.
DMF	Dimethyl fumarate
FDA	United States Food and Drug Administration
FOF	Defendants’ Post-Trial Findings of Fact
FP	Forward Pharma
ICH	International Conference on Harmonization
MMF	Monomethyl fumarate
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
Nilsson	International Patent Application Publication No. WO 2006/037342 (DTX324)
POSA	Person of ordinary skill in the art
PTAB	Patent Trial and Appeal Board
PTO	United States Patent and Trademark Office
tid	Three times daily dosing

I. INTRODUCTION

Biogen repurposed its application directed to a drug discovery research plan to cover something completely different—a specific dose (480 mg/day) of a specific drug (DMF) for a specific disease (MS). Biogen did so only *after* it had rejected 480 mg/day for its Phase II and proposed Phase III clinical trials, whereupon the FDA advised that Biogen test it to determine its effectiveness. This repurposing created multiple invalidity problems for the asserted '514 patent.

First, the '514 patent is invalid for lack of written description. A POSA would understand the specification to be directed to discovering new compounds to treat a variety of diseases, using screening assays that demonstrate activity on the Nrf2 pathway. It is not at all directed to dosing DMF to treat MS. Indeed, the specification does not specifically describe or even mention 480 mg/day DMF to treat MS, much less 240 mg bid. Moreover, the specification presents no data about dosing efficacy for any drug or for any disease, let alone the very specific dose claimed. The sole mention of 480 mg/day DMF is in a section discussing ways in which future researchers can determine an appropriate dose of a discovered compound for an unspecified disease. The treatment of MS is not mentioned at all in that section, nor is the 480 mg/day dose singled out as efficacious. The 480 mg/day dose is disclosed as part of various dose ranges that includes doses that all agree were already known to be ineffective to treat MS. The mention of that dose is, at best, an invitation for future research. "Patents are not rewarded for mere searches, but are intended to compensate their successful completion." *Nuvo Pharms. v. Dr. Reddy's Labs. Inc.,* 923 F.3d 1368, 1381 (Fed. Cir. 2019). This Court should reject Biogen's attempt to work backward from the claims, via impermissible hindsight, "to derive written description support from an amalgam of disclosures plucked selectively from" their application, and instead hold the claims invalid for lack of written description. *Novozymes A/S v. DuPont Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013).

Second, and relatedly, the '514 patent is invalid for lack of enablement. A POSA, reading

the specification, would need to conduct extensive experimentation to find an effective dose of DMF to treat MS. The specification discusses the experimentation required in the dosing section, and without that experimentation, a POSA would only get to 480 mg/day (or 240 mg bid) based on the prior art, not what is in the patent. But the law is clear, "[i]t is the specification, not the knowledge of [a POSA], that must supply the novel aspects of an invention in order to constitute adequate enablement." *Genentech v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

Third, the '514 patent is invalid for derivation and improper inventorship. Dr. O'Neill had no involvement with the research described in the specification, nor its filing. Rather, he merely presented a research plan with a range of doses that may or may not work, including a 480 mg/day dose of DMF, to treat MS. This is not conception of a definite and permanent idea. Biogen rejected dosing 480 mg/day (240 mg bid) DMF as part of that plan, and Dr. O'Neill left the DMF research program before 480 mg was ever tested to see if it actually worked. Ultimately, it was only because the FDA suggested it that Biogen ever even investigated it.

Fourth, the claims are obvious. The prior art disclosed that DMF was effective to treat MS and narrowed the expected range of the lowest effective dose to be between 360-720 mg/day. Selecting 480 mg/day DMF within this known range is not inventive, but rather a natural result of routine optimization to balance efficacy, safety, and tolerability. Within this range, a POSA would have found 240 mg bid (480 mg/day) obvious because it was reasonably expected to be effective and would offer improved tolerability and patient adherence over 240 mg tid.

Finally, Biogen cannot have it both ways, first, by maintaining that the Phase II studies provide enough information to describe and enable a 480 mg/day dose, and second by asserting those same studies fail to render that dose obvious. Written description requires more disclosure than "merely render[ing] the invention obvious." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d

1336, 1352 (Fed. Cir. 2010). If the claims are sufficiently described and enabled based on the POSA's knowledge, as Biogen argues, they are also obvious and anticipated by the prior art.

II. ARGUMENT

A. The Asserted Claims Are Invalid for Lack of Written Description

The asserted claims lack written description. All claims share the combination of three elements: (1) treating MS; (2) with DMF; (3) at 480 mg/day. FOF 10. Written description operates to guard against precisely what happened during prosecution, "overreaching through the addition of [these] later-filed claims which were not contemplated by the original invention." *Purdue Pharma, L.P. v. F.H. Faulding and Co.*, 48 F. Supp. 2d 420, 431 (D. Del. 1999), *aff'd* 230 F.3d 1320, 1327 (Fed. Cir. 2000). "The essence of the written description requirement is that a patent applicant, as part of the bargain with the public, must describe his or her invention so that the public will know what it is and that he or she has truly made the claimed invention." *Nuvo*, 923 F.3d at 1376-77. The test is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad*, 598 F.3d at 1351. Possession is shown by disclosure, and thus "the test requires an objective inquiry into the four corners of the specification from the perspective" of a POSA "as of the filing date*." Id.* The specification must be viewed "from the proper vantage point of one with no foreknowledge of the specific…" subject matter claimed. *Novozymes*, 723 F.3d at 1349. A POSA, reading the specification as of the filing date, would have no idea that Biogen may later replace the original claims wholesale with the claimed method of treating MS with 480 mg/day DMF. FOF 7. From that proper vantage point, a POSA would be unable to divine from the specification that the inventors possessed this specific combination of elements.

1. The Patent Specification Is About Drug Discovery—Not a Specific Treatment of a Specific Disease with a Specific Dose

The specification is not about DMF to treat MS at a specific dose. Biogen's predecessor had already filed applications dating back to 1999 covering treating MS with DMF. FOF 14. To this day, Biogen still enjoys patent protection from claims covering the use of DMF to treat MS that issued from those applications. FOF 51. The specification acknowledges that DMF had already been "proposed for treatment of MS." FOF 14. That is why the specification uses DMF for a different purpose. The basis for the application was "the finding that DMF activates the Nrf2 pathway," which along with DMF's known neuroprotective effects "offers a rationale for identification of structurally and/or mechanistically related molecules that would be expected to be therapeutically effective for the treatment of neurological disorders, such as, e.g., MS." FOF 4. DMF was the "starting point" to find new treatments. FOF 15. As Dr. Lukashev, the sole inventor involved in preparing the specification, confirms, this rationale was "strictly for discovery ... at the early stage" to search for "novel compounds." FOF 14. "Although inventor testimony cannot establish written description support where none exists in the four corners of the specification, it illuminates the absence of critical description." *Nuvo*, 923 F.3d at 1381.

The specification discloses five methods directed to screening for new compounds that, like DMF, activate Nrf2, along with using those compounds to treat a variety of diseases. The Methods are not directed to any specific disease and do not mention any useful doses for any specific disease. FOF 5-6; *see also* 15-17. It is undisputed that the specification provides no data administering DMF to humans—let alone, data of 480 mg/day DMF to treat MS. FOF 22. The examples in the specification offer no help to describe the claims. As Dr. Lukashev explained, "[t]he nature of the data is such that it's on a different subject really," it has "nothing to do with efficacy in clinical disease" and "cannot be used to define clinical dosing." FOF 24. "[T]his type of data is never directly informing for the purposes of selecting therapeutic dose, not the right

models, not the right settings, not the right experiments." *Id*. While "examples are not always required to satisfy [written description], the lack of any disclosure of examples may be considered when determining whether the claimed invention is adequately described." *Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011). Here, the examples confirm that the specification is directed to drug discovery—not doses for MS.

The only part of the specification that discusses dosing sets forth a general research plan to be performed in the future to find a dose for any discovered drug without discussing any disease. FOF 31-32. The specification makes clear it is only providing general dosing considerations when it states that "[p]reliminary doses … and scaling of dosages for human administration is performed according to art-accepted practices." FOF 6, 31. It then goes on to state that the therapeutically effective dose can be determined initially from "cell culture assays," and then assessed in an "animal model," and eventually that data "can be used in formulating a range of dosages for use in humans." FOF 19. Critically, the dosing discussion then concludes with a number of ranges of doses that "can be" effective for unspecified diseases, indicating the work still needs to be done. *Id*. The specification does not state that any of these doses "will be" or "are" effective in any disease. *Id*. The specification adds qualifications that effective doses will "vary" based on a number of factors such as the condition of the patient and "severity of the medical condition," which the specification fails to address. *Id*. 31. This emphasizes the exploratory and provisional nature of the dosing ranges. "A reasonable understanding of [these paragraphs] is that the inventors … had not yet firmly concluded that fumarates at a particular daily dosage were in fact effective for treating the entire list of enumerated conditions, which included MS..." *FWP IP Aps v. Biogen MA, Inc.*, 749 Fed. Appx. 969, 975 (Fed. Cir. 2018) (finding no written description in similar "paragraph teaching possible daily dosages"). The dosing section further does not identify any particular

disease, among the more than 30 identified, to which these doses may apply. FOF 19. The sheer range of doses and diseases would inform a POSA that the application was not directed to any particular dose that is effective against any particular disease.

Biogen asks the Court to hone in on one particular DMF dose (480 mg/day) at the lower end of one range of doses among the several identified, and then apply that dose to MS. But the dosing passage does not mention MS, and identifies doses that a POSA would have understood to be ineffective against MS. *Id*. 33-34. Consequently, a POSA would not consider this passage to be directed to MS. Further, the specification neither differentiates 480 mg/day from any of the other identified doses and ranges, nor provides any statement or rationale leading a POSA to understand that 480 mg/day is an effective dose. *Id*. 34. "The disclosure of a broad range of values does not by itself provide written description support for a particular value within that range. Instead, where a specification discloses a broad range of values and a value within that range is claimed, the disclosure must allow one skilled in the art to immediately discern the limitation at issue in the claims." *Gen. Hosp. Corp. v. Sienna Biopharms., Inc.*, 888 F.3d 1368, 1372 (Fed. Cir. 2018) (citation omitted). And the specification never once suggests administering 240 mg bid. A POSA would not immediately discern from the specification that 480 mg/day is effective for MS (much less 240 mg bid), but would instead understand that the dose ranges may prove effective in one or more diseases upon further investigation. This section "'just represents a wish, or arguably a plan' for future research," and that is not enough. *Ariad*, 598 F.3d at 1356-57 (citation omitted).

2. The Claims Were Changed In 2011 To The Treatment Of MS With DMF At 480 mg/day Creating A Mismatch With The Specification

None of the original claims covered treatment of any particular neurological disease (MS) with any particular compound (DMF) at a particular therapeutic dose (480 mg/day). FOF 7. In 2011, after obtaining the Phase III results, Biogen repurposed Dr. Lukashev's application, from a

drug discovery research plan to a specific treatment for MS with 480 mg/day DMF. *Id*. In the process, Biogen struck the title, "Nrf2 Screening Assays…," and replaced it with "Treatment of Multiple Sclerosis." *Id*. This scenario, having "canceled all his pending claims and replaced them … creat[ed] a mismatch between the claims and the originally filed specification," and a written description problem. *Quake v. Lo*, 928 F.3d 1365, 1373 (Fed. Cir. 2019).

When repurposing, Biogen had to add Dr. O'Neill as an inventor. FOF 8. But there was a reason he was not an original inventor, the specification had nothing to do with his work. *Id*. 8, 43. He worked in clinical development, and was not involved in the drug discovery research disclosed in the '514 patent. *Id.* He also had nothing to do with drafting the specification. He did not recall seeing it before 2011, and made clear that he "would not write a sentence" like the one containing the sole reference in the specification to 480 mg/day as a part of a range. *Id*. 43. That is because the specification is directed towards a basic science researcher, not an MS clinician.[1] *Id*. 11.

Dr. O'Neill testified that his hypothesis regarding the "magnitude of the dose combined with a different frequency" was critical to his belief that 480 mg/day would work. *Id*. 26. But his hypothesis is not included anywhere in the specification. *Id*. To the contrary, the specification focuses only on the total daily dose, not the magnitude of a given dose, and suggests that frequency is unimportant, with the total daily dose optionally administered over various frequencies. *Id*. The sole sentence that addresses frequency merely states that "720 mg per day may be administered" in any of "2, 3, 4, or 6 equal doses," without any preference or instruction to choose among them.

[1] The disputed definitions of a POSA reflect the disconnect between the specification and the later issued claims. As the proper vantage point is taken from the filing date with no foreknowledge of the claims, *Novozymes*, 723 F.3d at 1349, the POSA would be a researcher engaged in basic science and drug discovery. FOF 11. The specification provides no instruction to a clinician, rather it defers "[t]he appropriate therapeutically effective doses" to "be selected by a treating clinician." *Id*. 31. Ultimately, however, under either definition, there is a lack of written description. *Id*. 13.

Id. The patent never even mentions the administration of 240 mg bid DMF as required in claims 4, 9, 13 and 16, and that is the only 480 mg/day regimen that has ever been proven to be safe and effective.[2] *Id*.

According to the case Biogen cited in closing, "written description is about whether the skilled reader can recognize that what was claimed corresponds to what was described." Tr. 914:18-20; *Alcon Research Ltd. v. Barr Labs. Inc.*, 745 F.3d 1180, 1191 (Fed. Cir. 2014). Here, the claims do not correspond to the specification, which was never about treating a specific disease with a specific compound at a specific dose. Rather, the specification is about methods for discovering novel treatments—new compounds, in a host of diseases, in doses to be determined.

3. Biogen's Attempt To Reconstruct The Claim Elements From Hindsight Is Contrary To Law

In cases such as this where a patentee provides only overbroad and generic disclosures, and then later asserts written description support for a species, the Court assesses whether the specification provides "blaze marks" to the species. *Purdue*, 230 F.3d at 1326-27. "[O]ne cannot disclose a forest in the original application, and then later pick a tree out of the forest and say 'here is my invention'.… [T]he blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure." *Id.* Among the billions of compounds, over 30 neurological diseases, general dosing ranges, and factors to evaluate in drug discovery, the specification must provide "blaze marks" that would lead a POSA to the specifically claimed invention, i.e., (1) treating MS, (2) with DMF (3) at a dose of 480 mg/day (240 mg bid). The specification blazes no such trail.

Instead, Biogen must take the prohibited path of working backwards from the subject

[2] Claims 1-3, 6, 8, 11-12, and 15 cover 480 mg/day administered by any dosing regimen despite there being no evidence that any regimen other than 240 mg bid is effective. In fact, it is undisputed that 360 mg and more in a single dose is intolerable, such that 480 mg once-daily is not viable. FOF 26. The patent never addresses these critical dosing schedule issues, however, which only confirms lack of possession and enablement of the full scope of the claims.

matter it later claimed. Specifically, Biogen starts with the three specific claim elements introduced in the claims in 2011 and "[s]eek[s] to derive written description support from an amalgam of disclosures plucked selectively" from the specification. *Novozymes*, 723 F.3d at 1349. But "[w]orking backward from a knowledge of [the claims], that is by hindsight," is improper. *Id.*

And that is precisely how Dr. Wynn approached written description. FOF 28. He "was asked to describe the three elements of the claims." *Id*. Then he went back through the specification and "look[ed] to see if these [claim] elements were described ... for the purposes of written description." *Id*. He found different places in the specification that separately said MS, DMF, and 480 mg/day. *Id*. 29. Similar to the expert in *Novoyzymes*, Dr. Wynn "in effect admitted that [his] testimony suffered from this flaw when [he] 'pointed to a part of the claim' and told the judge [he] was 'going back and finding if there's a written description for that' in the specification. With such an approach 'it is all very clear what route one would travel through the forest of the specification to arrive at the claimed invention.'" *Novozymes*, 723 F.3d at 1349.

This "superficial[]" search for "formal textual support for each individual limitation," rather than the invention "as an integrated whole" is improper. *Id.* None of the places Biogen or Dr. Wynn cites in the specification disclose the claimed combination as a unified whole. FOF 29. Indeed, "one searches … in vain for the disclosure of … any 'blaze marks' that would lead an ordinarily skilled investigator toward such a species among a slew of competing possibilities*."* *Novozymes*, 723 F.3d at 1349.

In true hindsight fashion, Dr. Wynn characterizes the sole paragraph that mentions 480 mg/day in a dose range as "the real meat" of the patent, notwithstanding (1) the lack of specificity for any particular disease or dose, (2) language directing future studies, and (2) the absence of data. FOF 29. But even he recognizes the ranges of doses identified may be applicable to the many

neurological diseases identified in the specification. *Id*. And all agree that there is no "one dose fits all" disease approach to dosing which further emphasizes that a POSA reading this disclosure of ranges without hindsight would not understand it as disclosing a specific dose for treating a specific disease as Biogen later claimed. *Id*.

Biogen attempts to fill this fatal gap by relying exclusively on prior art regarding DMF dosing for MS—the published results of its Phase II clinical trials. Biogen contends a POSA reading the specification would immediately understand 720 mg/day is effective for MS, and then infer that 480 mg/day would also be effective because it is "linked" in a range that includes 720 mg/day. FOF 34. There are multiple problems with this approach.

First, it is impermissible under controlling law: "a description that merely renders the invention obvious does not satisfy the requirement." *Ariad*, 598 F.3d at 1352. Biogen's argument for written description is an obviousness analysis based upon combining disclosures in the patent and the prior art. To combine disparate disclosures in the patent, Biogen takes "a satellite view of the patent" and concludes that it "sparkles with the light" of DMF in some places and "spark[les] also with MS" elsewhere. Tr. 923:13-19. Then Biogen adds to the combination the dosing section of the '514 patent, choosing MS among more than 30 listed neurological diseases, and identifies a "deliberate sort of funneling down to the narrow[ed] range of 480 to 720." Tr. 925:22-926:1. As part of this analysis, Biogen must rely upon prior art to "link [the range] to the known effective dose of 720 milligrams per day." FOF 34. Tellingly, to get to the "lower endpoint … 480" of the narrowest range, Biogen refers "back to the minimally effective dose comments" from Defendants' obviousness analysis, *not* the specification. Tr. 926:1-2; *see* Infra. "[S]uch necessary picking and choosing to arrive at the claimed invention may indicate obviousness of the now claimed subject matter but does not indicate it was described." *Biogen MA Inc. v. Forward Pharma A/S*,

Interference No. 106,023 at 27 (PTAB Mar. 31, 2017), *aff'd* 749 Fed. Appx. 969 (Fed. Cir. 2018).

Second, Biogen's obviousness theory for written description is factually wrong. The specification also describes ranges including 720 mg/day that a POSA would have known included doses not effective to treat MS. FOF 34. Biogen had already published that doses of 360 mg/day and lower were not effective. *Id*. 33. The lower ends of three of the four disclosed ranges (0.1-1 g/day; 200-800 mg/day; 240-720 mg/day) were known to be ineffective in MS. *Id*. The ineffective 240 mg/day dose is "linked" to 720 mg/day in the same way as 480 mg/day. *Id*. Accordingly, a POSA would have no reason to believe the ranges were directed to MS, let alone that the lower bound of the fourth range (480 mg/day) would be effective in treating MS.

Third, a POSA would understand the absence of the Phase II studies in the specification to confirm that it was not about MS. FOF 22. If the '514 patent was actually about clinical doses for MS, nothing would be more relevant than the only dose-ranging clinical studies, which a POSA would see is glaringly missing. *Id*; *see Novozymes*, 723 F.3d at 1349 ("[I]f Novozymes had possessed a working variant substituted at position 239, it surely would have disclosed that substitution instead of, or at least along with, the nonfunctional S239W substitution in the several pages of the 2000 application devoted to listing exemplary substitutions."). Biogen cannot backfill its deficient specification through hindsight. It violates both the law and the facts.

4. Biogen Is Bound by Its Arguments to The Patent Office That Confirm Lack of Written Description

The arguments Biogen during prosecution only magnify the inadequacy of the written description. "The patentee is bound by representations made and actions that were taken in order to obtain the patent." *Typhoon Touch Techs., Inc. v. Dell, Inc.*, 659 F.3d 1376, 1381 (Fed. Cir. 2011). "[A] patentee's representations to the PTO during the prosecution of its patent application about the scope of the prior art is a binding admission and should 'be accepted at face value' during

subsequent litigation." *P&G v. Nabisco Brands, Inc.*, 711 F. Supp. 759, 770 (D. Del. 1989) (internal citation omitted).

To overcome an obviousness rejection of the asserted claims and to secure their allowance, Biogen argued that it was unexpected that 480 mg/day DMF was effective to treat MS in view of the Phase II results. FOF 36. "A [POSA] would not have expected a dose of 480 mg/day to be effective in treating MS." DTX457_3115; *id.* 3146 (A POSA "would not have a reasonable expectation that the 480 mg/day dose would provide statistically significant and clinically meaningful effectiveness for treating MS."). Both of Biogen's MS clinician experts agreed. FOF 35, 37. Biogen cannot rely on the Phase II studies to show possession of the invention while simultaneously contending those studies would have indicated to a POSA that the claimed invention would not work. In fact, Dr. Wynn admitted that if "he had seen this patent in 2007," he "wouldn't know if [the 480 mg/day dose] was clinically effective" and even "upon reading the '514 application" he would be "terribly surprised" if that dose would exhibit "clinical efficacy or statistically have an effect ... in a Phase III trial." *Id*. 35. Dr. Wynn goes so far as to say the prior art "would effectively teach away from the invention," because a POSA "would go to 720 [mg/day] or higher [as] that was the lowest effective dose in the Phase II study." *Id.* Taking Biogen's representations at face value, "the record evidence demonstrates that a person of ordinary skill in the art would not have known or understood that [480 mg/day] is effective." *Nuvo*, 923 F.3d at 1380.

Biogen contends its statements are in the context of analyzing obviousness "before reading the patent," Tr. 918:8-14, but the specification provides "no new information" to a POSA—no data for 480 mg/day, no dose-response curve, and no theories or explanations. FOF 38. It merely suggests, among a multitude of options, a range of 480-720 mg/day for no particular use. FOF 30-

31. At best, a POSA is left to presume, like Dr. Wynn did, that "the inventor knows [information that he's] not privy to and is not included in the specification." *Id*. 38. That is antithetical to "possession as shown in the disclosure" as written description requires. *Ariad*, 598 F.3d at 1351.

Biogen attempts to maneuver around this problem by arguing that 480 mg/day DMF is listed in the context of a specification focused on MS. This is not how a POSA would understand the specification; but even if true, this is not enough. The Federal Circuit has "expressly rejected the 'argument that the written description requirement ... is necessarily met as a matter of law because the claim language appears *in ipsis verbis* in the specification.'" *Nuvo*, 923 F.3d at 1380 (citation omitted). In instances like this case, when "the specification provides nothing more than the mere claim that [the claimed subject matter] might work, even though persons of ordinary skill in the art would not have thought it would work, the specification is fatally flawed. It does not demonstrate that the inventor possessed more than a mere wish or hope that [the claimed invention] would work, and thus it does not demonstrate that he actually invented what he claimed." *Nuvo*, 923 F.3d at 1381 (holding that the recitation of "typical dosage amounts" and "calling generally for effective amounts" is not "enough to satisfy the written description requirement").[3]

5. The '514 Patent Specification Lacks Sufficient Written Description For The Same Reasons Biogen Has Previously Argued

The written description for the asserted claims in the '514 patent fails for the same reasons Biogen successfully argued with respect to Forward Pharma's ("FP") specification in Interference

[3] Biogen's attempt to distinguish *Nuvo* as a case in which "the specification and claims were in direct conflict" is unconvincing. Biogen suggests the Court determined that the specification taught that the claimed uncoated PPI "would not work," Tr. 915:21-916:8, when the Court only stated that PPIs are "coated to avoid destruction by stomach acid." *Nuvo*, 923 F.3d at 1373-74. The Court never references any "direct conflict" and instead focuses on what was known to the POSA: that "***the prior art*** taught away from such effectiveness." *Id.* at 1376. The Court also relied upon the district court's finding "upon [the patentee's] insistence as part of ***its obviousness analysis*** that ordinary skilled artisans would not have expected uncoated PPIs to be effective, and nothing in the specification would teach a person of ordinary skill in the art otherwise." *Id.* at 1377.

No. 106,023. That interference involved "claims substantially copied from Biogen's ['514] patent" involving the combination of the same three elements of (1) treating MS; (2) with DMF and/or MMF; with (3) a therapeutically effective amount of 480 mg/day. *Biogen MA Inc. v. Forward Pharma A/S*, Interference No. 106,023 (P.T.A.B. Mar. 31, 2017) at 1, 19. Biogen argued those claims were "not supported by … an adequate written description" in FP's specification. *Id.* at 2. The PTO agreed:

> We think (1) the focus of FP's specification on controlled release fumarates to reduce gastrointestinal impact compared to prior art fumarate compositions and (2) the general teaching of the applicability of fumarates to treatment of a variety of possible diseases or conditions and the teaching of a broad range of possible dosages would not have conveyed possession or description of the specific treatment of MS that FP now claims.

Id. at 3. The '514 patent specification is striking in its parallels to the FP specification. Neither "reveal[s] an express description of a method that includes the specific elements … connected as required by the claims…" *Id.* at 19. Neither focuses on treating MS with a given dose—FP focuses on "controlled release compositions," (*id*. at 9) whereas Biogen focuses on discovering new treatments for neurological diseases. FOF 4. In the FP specification, 480 mg/day is "mentioned three times in the disclosure, i.e. as both the low and high end of ranges within the broader range of 240 to 1080 mg/day." *Id.* at 22. But like the '514 patent specification, "the written description does not indicate 480 mg/day is a therapeutically effective dose with respect to any condition or disease or is otherwise of any particular significance with respect to the treatment of MS…" *Id.*

FP appealed to the Federal Circuit. *FWP IP*, 749 Fed. Appx. at 970. Biogen's written description arguments on appeal are equally applicable to the '514 patent. FOF 39. According to Biogen, the FP specification "indiscriminately lists doses ranging from 240 mg to 1080 mg … and it states that the daily dosage depends on a number of factors including the 'condition or disease to be treated.' .... FP provides no guidance to select a 480 mg/day dose over any of the other

amounts for any disease, much less for MS specifically." DTX377_0026. The Federal Circuit affirmed, and found "[f]or the same reasons set forth by the Board" that the specification "does not disclose the now-claimed MS treatment as a unified whole." *FWP IP*, 749 Fed. Appx. at 974.

6. There is No Constructive Reduction To Practice Of The Claimed Elements

Since the specification never discloses any "experimental data," any "theory or explanation of how or why [480 mg/day] will be effective," or any actual reduction to practice, *Nuvo*, 923 F.3d at 1380, Biogen argues that "480 to 720 is essentially a constructive reduction to practice of 480 milligrams." Tr. 926:5-8. That argument is circular. For constructive reduction to practice, the specification must disclose the invention in compliance with 35 U.S.C. § 112. *Storer v. Clark*, 860 F.3d 1340, 1344-45 (2017). "Constructive reduction to practice means a described and enabled anticipation" of the claimed subject matter. *Id.* There is no constructive reduction to practice here because there is no written description support. *See Goeddel v. Sugano*, 617 F.3d 1350, 1351 (Fed. Cir. 2010) ("That the [claimed invention] could have been 'envisioned' does not establish constructive reduction to practice…"); *Bigham v. Godtfredsen*, 857 F.2d 1415, 1417-18 (Fed. Cir. 1988) (disclosure of "halogen," commonly understood to be limited to 4 species (i.e., chloro, bromo, iodo and fluoro), not a constructive reduction to practice "of the bromo and iodo species").

If the '514 patent was truly about a specific dose of DMF to treat MS, the specification could have disclosed a constructive reduction to practice by describing the claimed subject matter as a specific combination of 480 mg/day of DMF for efficacy in MS. This is clear because Biogen later did so with a different patent application identifying Drs. O'Neill and Dawson as inventors, which only emphasizes the lack of description in the specification of the '514 patent. FOF 40.

7. The Examiner's Failure To Raise Written Description Does Not Negate The Clear And Convincing Evidence Of Lack Of Written Description

It is not uncommon for courts to invalidate patents for lack of written description during

litigation, which necessarily means the PTO missed the issue.[4] The recent vitality of written description is shown by several notable reversals by Federal Circuit within the past year. *Nuvo*, 923 F.3d at 1384; *Idenix Pharms, LLC v. Gilead Scis., Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019) (holding the specification "fails to provide sufficient blaze marks to direct a POSA to the specific subset of [compounds] that are effective in treating HCV" despite "lists [and] examples of supposedly effective nucleosides but do not explain what makes them effective, or why.").

The prosecution history indicates that the written description issue was missed, despite the examiner making findings warranting such a rejection. FOF 9. In particular, in support of an obviousness rejection, the examiner stated that "***the particular combination now claimed***" was not "described in the specification as filed." DTX12_0891 (emphasis in original). And referring to the daily dosage paragraph of column 18, the examiner commented that "the instant specification, as filed, fails to suggest any specific daily dosage of DMF or MMF that had been shown or could reasonably be predicted to be effective in the treatment of MS, in particular. The only dosages described in the specification were identified therein as being applicable to the treatment of the whole variety of neurological diseases." DTX12_0893. Despite those findings, which were never disavowed, a written description rejection was not raised. FOF 9. The examiner incorrectly treated the issue as one of obviousness. *Id*. The prosecution history supports, rather than detracts from, the lack of written description.

B. The Asserted Claims of The '514 Patent Are Invalid for Lack of Enablement

[4] As Biogen's counsel has published, "the patent owner will always argue that the issue … had to have been considered by the patent examiner in allowing the claim in the first place." Finnegan - Charles E. Lipsey, "Litigation of the Written Description," June 22-25, 2005, available at https://www.finnegan.com/en/insights/litigation-of-the-written-description.html. Nonetheless, counsel also recognizes that "[t]he cases are legion where failure to comply with the written description requirement has resulted in invalidation of patent claims…" *Id.*

The specification fails to enable the asserted claims for many of the same reasons it does not adequately describe them. *Ariad*, 598 F.3d at 1352 ("[W]ritten description and enablement often rise and fall together").[5] "[P]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." *In re '318 Patent*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) (citation omitted). It is not enabling for a "specification [to provide] only a starting point, a direction for further research." *Genentech*, 108 F.3d at 1366. That is precisely what the specification provides, a "starting point" from which a POSA could "look for compounds that activate the Nrf2 pathway." FOF 15. And the ranges of doses provided for DMF that "can be" effective would simply be understood as "a range of doses that [the inventors] want to try in the future or that [a] clinician can explore." FOF 20.

"To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Alza Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010) (citation omitted). The Federal Circuit has set forth eight factors that the Court may consider, which in this case, support that undue experimentation would be necessary to practice the claimed invention:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). Because the specification discloses only a "research plan," the quantity of experimentation necessary to determine which doses are effective against which diseases is left entirely to the POSA. FOF 31. The specification generally explains the significant experimentation a POSA would have to undergo in going from "in vitro assays or

[5] For this reason, Defendants incorporate by reference their factual and legal arguments for written description into their discussion of enablement, and vice versa.

animal studies" to "a range of dosages for use in humans." *Id*. 19; DTX1_0023 (18:14-16). There is no direction or guidance, or any working examples, that would inform a POSA that 480 mg/day, much less 240 mg bid, DMF is effective for treating MS. FOF 27. Because the specification provides "no new information" about "using DMF to treat MS at a particular dose," a POSA would have to rely on what was already known by those skilled in the art. FOF 38. Thus, to the extent the claims are not invalid as obvious, this work would have been beyond the level of ordinary skill. In addition, "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." *Genentech*, 108 F.3d at 1366. The purportedly novel aspect of the asserted claims is a therapeutically effective dose of 480 mg/day DMF for treating MS, which is not enabled by the patent specification.

C. The Asserted Claims Are Invalid for Improper Inventorship and Derivation

A person is not entitled to a patent if "he did not himself invent the subject matter sought to be patented." 35 U.S.C. § 102(f). Undisputedly, Dr. Lukashev, the sole inventor of the original application, did not invent the claimed method of treatment. FOF 2, 8. It is thus unsurprising that his application failed to describe or enable the claims, when he admits that his work had "nothing to do with [] efficacy in clinical disease" and "cannot be used to define clinical dosing." *Id*. 7, 24.

In 2004, Dr. O'Neill did propose 480 mg/day (240 bid), but only among other doses including 120 mg/day, 240 mg/day, 360 mg/day, 720 mg/day, and 1080 mg/day, in four dosing options that could be tested in Biogen's Phase II clinical trial. *Id*. 42. Dr. O'Neill preferred Option 1 not because it contained 480 mg/day, but because he believed that the combination of doses was the "most scientifically rigorous" and would have enabled him to probe his hypothesis that dose frequency might impact efficacy. *Id*. 49. But his colleagues overruled him. *Id*. Thus, his research plan was not performed and his hypothesis about dose frequency remained just that—a hypothesis. This is not conception. Conception requires "the formation in the mind of the inventor, of a definite

and permanent idea of the complete and operative invention," which means that "the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue." *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994) (citations omitted). Dr. O'Neill did not even know whether DMF would be effective to treat MS, let alone at a particular dose or dose frequency. FOF 42. He thought all of the doses identified "could" be effective, including each of 120, 240, and 360 mg/day. *Id*. As with these other doses, he had "no more than a hope, or wish" that any dose, including 480 mg/day, would be effective, but "[s]uch a bare hope is insufficient to establish conception." *Hitzeman v. Rutter*, 243 F.3d 1345, 1357 (Fed. Cir. 2001).

Before the 2006 results of the Phase II clinical trial, those at Biogen were already operating under "the commercial constraint" that "720 mg is the only viable dose." FOF 44. Biogen had effectively abandoned the idea to test 480 mg/day. And the ineffectiveness in Phase II of two doses (120 and 360 mg/day) that Dr. O'Neill thought "could" be effective (*id*. 42) only further demonstrated that his beliefs of potential efficacy were conjecture and his purported conception was incomplete. *Burroughs*, 40 F.3d at 1229 ("A conception is not complete if the subsequent course of experimentation, especially experimental failures, reveals uncertainty that so undermines the specificity of the inventor's idea that it is not yet a definite and permanent reflection of the complete invention as it will be used in practice."). In fact, Biogen, Drs. Dawson, Duddy and Wynn agreed that at the time the '514 patent was filed, 480 mg/day would not have been expected to be effective in view of the ineffectiveness of 360 mg/day in the Phase II trials. FOF 35-37.

While Dr. O'Neill now maintains, almost 15 years later, that he always thought 480 mg/day "would" work, there is simply no contemporaneous evidence. *Id*. 42. The contemporaneous evidence showed that he preferred Option 1 generally (not 480 mg/day), and after Option 1 was

rejected, Biogen was intent on pursuing only 720 mg/day. FOF 44. Dr. O'Neill left the DMF program before a decision on dosing for the Phase III trials had been made. *Id*. 43. At that time, 480 mg/day was only discussed as a "contingency plan," if the FDA disagreed with Biogen's proposed dose of 720 mg/day. *Id*. 45. Biogen did everything it could to avoid that "contingency plan" by omitting it from the materials sent to the FDA and avoiding discussion of that dose with the FDA. *Id*. 45-46.

In spite of this, reviewers at the FDA independently advised adding "intermediate doses in the Phase 3 study, e.g. 240 mg b.i.d. or 120 mg t.i.d." DMF to treat MS. *Id.* 46. In September 2006, Biogen relented and added 240 mg bid DMF to the Phase III study "based on feedback from FDA." *Id*. 47. The claimed invention was derived from the FDA's "prior conception of the invention" and "communication of that conception" to those at Biogen, including Dr. Lukashev. *Gambro Lundia AB v. Baxter Healthcare Corp*., 110 F.3d 1573, 1576 (Fed. Cir. 1997). But for the FDA's independent conception and guidance to Biogen, 480 mg/day would never have been tested. FOF 45-47. It was only after obtaining the results of the first Phase III study that Biogen improperly repurposed Dr. Lukashev's application and added Dr. O'Neill as an inventor. FOF 40. This constitutes derivation from the FDA, or at a minimum, improper inventorship for failing to recognize the contribution to conception by those at the FDA. *Pannu v. Iolab Corp*., 155 F.3d 1344, 1349 (Fed. Cir. 1998) (providing that invalidity for failure to name a proper co-inventor).

Dr. O'Neill, who did not contribute to Dr. Lukashev's work disclosed in the specification or preparing the application, was improperly added as an inventor. FOF 43. "The alleged joint inventor seeking to be listed on a patent must demonstrate that his labors were conjoined with the efforts of the named inventors," because joint inventorship "can only arise when collaboration or concerted effort occurs." *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1359 (Fed. Cir. 2004).

That Dr. O'Neill allegedly conceived of the full invention in 2004, independent of Dr. Lukashev, shows there was no joint inventorship and constitutes improper inventorship. *Swanson v. Alza Corp.*, No. 12-cv-4579, 2015 WL 1304436, at *12 (N.D. Cal. Mar. 20, 2015).

D. The Asserted Claims of The '514 Patent Are Obvious

A patent may not issue "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (pre-AIA). The '514 patent fails to meet this nonobviousness requirement.[6]

DMF was known in the prior art to effectively treat MS. FOF 50. And per ICH guidelines, a POSA would have sought to determine the lowest effective dose of DMF to treat MS. *Id*. 62. Biogen's Phase II study narrowed the expected range for the lowest effective dose to 360-720 mg/day. Thus, the only claimed difference from the prior art is an intermediate dose of 480 mg/day DMF, which was squarely within the known dose range. *Id.* at 69. Selecting this dose would have been obvious in view of the Phase II study. "[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness." *Tyco Healthcare Grp. LT v. Mut. Pharm. Co.*, 642 F.3d 1370, 1372 (Fed. Cir. 2011). It would have been routine to optimize the DMF dose within this range, with a reasonable expectation of treating MS. FOF 62-68. The asserted claims of the '514 patent therefore are obvious. *Id.* 48.

1. A POSA Would Have Been Highly Skilled

Both parties assessed obviousness of the claimed invention from the perspective of a

[6] The Federal Circuit has made clear that a claim can be both obvious and not adequately described, even when the description would render the claim obvious. *Ariad*, 598 F.3d at 1352 ("[D]escription that merely renders the invention obvious does not satisfy the requirement."). But, at a minimum, if the Court finds the asserted claims adequately described, they are obvious for the same reason.

POSA, who as of February 8, 2007, has an M.D., at least 3 years of training in neurology, and at least 3 years of clinical experience treating MS. *Id*. 49.

2. The Scope and Content of the Prior Art Teach All Claim Limitations

The named inventors were not the first to discover a "method of treating a subject in need of treatment for [MS] comprising orally administering to the subject in need thereof a pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of [DMF and/or MMF], and (b) one or more pharmaceutically acceptable excipients." *Id.* 70. Nearly eight years before the priority date, in July 1999, Joshi filed a patent application covering "[a] method of treating multiple sclerosis" by "treating a patient ... with an amount of … [DMF] effective for treating [MS]." *Id*. 50-51. This would have guided a POSA to focus on treating MS with DMF, and would have motivated them to further define the amounts of DMF effective for treating MS, including by reviewing the prior art clinical studies of DMF. *Id.*

A POSA would have been aware of Biogen's Phase II study—a 48-week "dose-ranging" study of DMF in 257 MS patients. *Id.* 52-53. Patients were given placebo or doses of DMF at 120 mg/day (120 mg qd), 360 mg/day (120 mg tid), or 720 mg/day (240 mg tid). *Id.* In January 2006, Biogen announced that the Phase II study had "met its primary endpoint" of significantly reducing MRI brain lesions. *Id.* 55-56. This would have informed a POSA that one or more of the DMF doses were effective to treat MS. *Id.* Within this range of 120-720 mg/day DMF, it would not have been "inventive to discover the optimum or workable ranges by routine experimentation." *Genentech, Inc. v. Hospira, Inc.*, No. 2018-1933, 2020 WL 111268, *6 (Fed. Cir. 2020). Indeed, the prior art (*e.g.*, Nieboer 1990 and Nilsson) taught administering 480 mg/day DMF (240 mg bid) to treat psoriasis and other autoimmune diseases, such as MS. FOF 63.

In May 2006, Biogen publicly presented additional Phase II results, which further narrowed the therapeutically effective dose range. *Id*. 56, 67. While 720 mg/day DMF was shown to be

effective, 120 and 360 mg/day exhibited only a trend but not a statistically significant reduction in MRI brain lesions. *Id.* Although all three DMF doses exhibited comparable safety, there were dose-related tolerability issues as expected, particularly GI-related issues. *Id.* 57-58. These adverse events can impact DMF's tolerability and limit long-term treatment. *Id.* In light of these Phase II results, a POSA would have been motivated to find the lowest effective DMF dose, which a POSA would have reasonably expected to be between 360-720 mg/day. *Id.* 62-64, 66-68.

At trial, Biogen argued that the Phase II study results presented in May 2006—*i.e.*, Kappos Presentation 2006, Kappos Abstract 2006, and Biogen Press Release May 2006 (DTX329, DTX327, DTX441)—do not qualify as prior art, because they are the inventors' own work. PDX008-31. Biogen's argument is meritless. To determine whether a publication is "by others" under § 102(a), the "relevant inquiry" is whether it is "solely [the inventor's] work and hers alone." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 969 (Fed. Cir. 2014). In *Allergan*, as is the case here, articles describing clinical trial results were found to be § 102(a) prior art, because they listed several co-authors contributing to the clinical trials. *Id.* And even if the named inventor had alone "supervised the logistics of the clinical trial," she was not solely "responsible for directing the production of either article's content, which includes the design, trial, and analysis of results." *Id.* The 2006 Phase II study publications similarly are not exclusively Dr. O'Neill's work, but reflect the work of "others," his co-authors. FOF 59. For instance, Dr. Kappos, "as chair of [the Phase II] study's steering committee," is accredited with drafting the clinical study protocol and statistical plan, overseeing the conduct of the study, reviewing the statistical analysis, and publication. *Id.* Dr. Kappos and the other listed coauthors contributed far more than the coauthors in the cases Biogen cites. *See In re Katz*, 687 F.2d 450, 452 (C.C.P.A. 1982) (the coauthors "were students working under…the inventor"); *Eli Lilly Co. v. Teva Pharms.*, 657 F. Supp. 2d 967, 991 n.18, 1013

(S.D. Ind. 2009) (the contributions of the coauthors were limited to clinical site recruitment, statistics, and formatting the article); *Mannesmann Demag Corp. v. Eng'g Metal Prods. Co.*, 605 F. Supp. 1362, 1370 (D. Del. 1985) (only the named inventor contributed to the publication). As the Phase II study publications derive from collaborations with non-inventors—not solely Dr. O'Neill—they constitute § 102(a) prior art.

In addition, Biogen repeatedly argued to the PTO that these May 2006 Phase II publications were prior art to support unexpected results. FOF 60. Biogen is bound by its "representations to the PTO during the prosecution of its patent application about the scope of the prior art." *P&G,* 711 F. Supp. at 770. Biogen cannot use these results as prior art to obtain the patent during prosecution, and now argue that they are not prior art in litigation. Regardless, as discussed below, the asserted claims still would have been obvious even relying solely on the § 102(b) prior art.

3. A POSA Would Have Been Motivated to Administer 480 mg/day DMF to Treat MS with a Reasonable Expectation of Success

a. A POSA Would Have Sought the Lowest Effective Dose

In view of the Joshi References and the Phase II study, a POSA would have been motivated to find the "lowest effective dose of DMF." FOF 62-65. ***First***, as Dr. Stobbe explained, it was widely understood that using the lowest effective dose increases "the likelihood ... [of] controlling or reducing side effects," and improves "tolerability and adherence." *Id.* 62. The ICH Guidelines on the "design of clinical trials" confirm this motivation. *Id*. They teach that "[h]istorically, drugs have often been initially marketed at what were later recognized as excessive doses ... sometimes with adverse consequences," but this has been improved with "find[ing] the smallest dose with a discernable useful effect or a maximum dose beyond which no further beneficial effects is seen." *Id*. A POSA would have been motivated to optimize drug dosing and administration parameters to balance efficacy, safety, tolerability, and adherence. *See, e.g., Sciele Pharma, Inc. v. Lupin Ltd.*,

684 F.3d 1253, 1262 (Fed. Cir. 2012) (a POSA would have been motivated by the benefits of "reduction in dosing frequency, providing patient convenience that would probably improve compliance" as well as "an extended time period over which therapeutically beneficial plasma levels of drug were maintained."); *Purdue Pharma. Prods. L.P. v. Actavis Elizabeth LLC*, No. 12-cv-5311, 2015 WL 5032650, at *36 (D.N.J. Aug. 25, 2015) (A POSA "would undoubtedly attempt to find the lowest effective dose of zolpidem to avoid potential residual sedative effectives.").

Second, a POSA would have also been motivated to find effective doses lower than 720 mg/day (240 mg tid) in order to allow for fewer administrations. FOF 63. Several studies have shown that "that once or twice daily regimens are associated with better [patient] adherence" than thrice daily dosing. *Id.* As Dr. Stobbe explained, minimizing the frequency of administration is "important, especially if you're treating a chronic condition like [MS]." *Id*.

b. The Phase II Study Narrowed the Expected Therapeutically Effective Dose Range of DMF, Including 480 mg/day

A POSA would have reasonably expected based on the Phase II study design and results published by January 2006 that the lowest effective DMF dose to treat MS would range within 120-720 mg/day. FOF 66. A POSA would have known that one or more of 120, 360, or 720 mg/day DMF had met the study's primary endpoint for significantly reducing MRI brain lesions. *Id.* A POSA would have been motivated to determine the optimal DMF dosage, including selecting 480 mg/day DMF, with a reasonable expectation of treating MS. *Id.; Tyco Healthcare Grp.,* 642 F.3d at 1372 ("[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness."); *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737-38 (Fed. Cir. 2013) (explaining that in such circumstances "the burden of production falls upon the patentee to come forward with" evidence of pertinent secondary considerations). "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to

discover the optimum or workable ranges by routine experimentation." *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018).

The Phase II results presented in May 2006 added more dose-response information of DMF to treat MS, which would have further focused a POSA to 360-720 mg/day DMF as the expected range of the lowest effective dose. FOF 67. In view of the additional efficacy, safety, and tolerability data from the Phase II study, a POSA would have sought to administer intermediate DMF dosages within this range, with a reasonable expectation of efficacy. *Id.*

Additionally, a POSA would have been particularly motivated to try 480 mg/day DMF. Since the Phase II study used 120 mg DMF capsules, this would have left a POSA with only three doses of 480, 600, and 720 mg/day of DMF to test to confirm the lowest effective DMF dosage. *Id.* As Dr. Stobbe explained, since 480 mg/day has the added patient adherence benefit of twice-daily dosing of 240 mg (the maximum DMF administered at one time in the Phase II study), this dose would have been a "very logical choice." *Id*. The Phase II study thus would have directed a POSA to choose from this "finite number of identified, predictable solutions." *KSR*, 550 U.S. at 421. Because a POSA would have had "good reason to pursue the known options within his or her technical grasp," it would have been obvious to try a 480 mg/day (240 mg bid) DMF dose to treat MS, as "the product not of innovation but of ordinary skill and common sense." *Id.*

Biogen argues that a POSA would not have been limited to the 120 mg increments that were used in the Phase II study, as theoretically any DMF strength dosage form could be used. But the Phase II study's use of 120 mg increments would have influenced a POSA to continue to build upon the known increments. FOF 67. For instance in, *In re Copaxone Consolidated Cases*, "[a]lthough the universe of potential GA doses is theoretically unlimited, the universe of dosages in the prior art that had clinical support for being effective and safe consisted of only two doses:

20mg and 40mg." 906 F.3d 1013, 1026 (Fed. Cir. 2018). "Even if there were multiple injection frequencies not yet tested in the prior art—1x, 2x, 3x a week etc.—these still represent a limited number of discrete permutations," so a "thrice-weekly dosing regimen of 40 mg GA [was] obvious to try." *Id.* Here, in view of the focus on doses of 120 or 240 mg DMF in any single administration during the Phase II study, constrained by the known lowest effective dose lying in the range of 360-720 mg/day, it would have been obvious to try 480 mg/day DMF, the only dose that would follow the 120 mg paradigm and permit twice daily dosing. *See also Hoffmann-La Roche Inc. v. Apotex Inc.*, 496 F. A'ppx 46, 51 (Fed. Cir. 2012) (finding no clear error from relying on a "trend[] towards intermittent dosing based on the total dosing concept" to find a finite number of identified, predictable solutions). Inventors are not rewarded with patents by "merely us[ing] routine research methods to prove what was already believed to be the case." *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1363 (Fed. Cir. 2007). Beyond the Phase II study, based on the prior studies, the prior art consistently taught administering DMF in doses of 120 mg increments, and how to make DMF oral capsules in these increments. FOF 67.

c. The Prior Art Did Not Discourage 480 mg/day DMF

Dr. Duddy opined that the Phase II study results would have "steer[ed]" a POSA to try only higher (not lower) doses than 720 mg/day. FOF 65. He reasoned that nothing in the Phase II study "show[ed] that we have maxed the idea of efficacy" or "reached a ceiling of tolerability." *Id.* That is, the side effects had yet to reach the level of "dangerous or prohibited," so 720 mg/day is not yet at the "breaking point" for tolerability to be unsafe. *Id.*

A POSA would not have been limited to Dr. Duddy's singular focus on maximizing efficacy up to the tolerability ceiling. While doses above 720 mg/day DMF could show greater efficacy, higher doses would require either more frequent daily administration (more than 3-times daily) and/or larger individual doses, both of which increase the likelihood of "dose-related side

effects," e.g., flushing and GI side effects, which can be particularly problematic for a chronic treatment. Id. 64. When considering life-long treatment for a progressive disease like MS, many patients prefer treatments that prioritize safety, tolerability, and adherence. *Id.* 65. In fact, the MS treatments at the time showed that the "bulk of people" preferred the less effective but more tolerable first line treatments (like interferons) than the more effective but less tolerable or safe second line treatments (like infusions). *Id.* A POSA would have been motivated to develop DMF as the first "oral medication" to target this larger market for a "front-line" MS therapy. *Id.*

Not surprisingly, Biogen presents no contemporaneous evidence supporting Dr. Duddy's opinion that Phase II study would have steered a POSA to try only doses higher than 720 mg/day. To the contrary, Biogen clearly understood the motivation to identify the lowest effective dose at the time and formed a contingency plan that included 480 mg/day if the FDA was unsatisfied that Biogen "had demonstrated a minimally efficacious dose." FOF 45. And despite Biogen's attempt to avoid a lower dose, the FDA advised "testing intermediate doses in the Phase 3 study, e.g. 240 mg b.i.d. or 120 mg t.i.d.," which "might improve patient compliance and/or minimize dropouts from adverse effects during the study." *Id.* 46. The FDA's advice is contemporaneous evidence that skilled artisans were motivated to test a dose of 480 mg/day, and contradicts Dr. Duddy's opinion that a POSA would have been solely motivated to try higher doses than 720 mg/day. *See Copaxone*, 906 F.3d at 1030 (finding no error in the district court's reliance on non-prior art for the "limited purpose" of "evidence of a POSITA's motivations and expectations.").

But even under Dr. Duddy's premise that a POSA would have pursued higher daily doses, this does not negate the motivation of a POSA pointing towards finding the lowest therapeutically effective dose. The Federal Circuit's "case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide

motivation for the current invention." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). The prior art reflected a clear motivation to find the lowest effective dose. FOF 62, 64.

d. Absolute Predictability of Efficacy Is Not Required

In the end, the crux of Dr. Duddy's opinion is that a POSA would "know nothing" about efficacy between 360-720 mg/day. *Id.* 65. He alleges "complete ignorance" before and after the "one data point" at 720 mg/day. *Id.* But, "[c]onclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success." *Hoffmann La Roche, Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014); *Copaxone*, 906 F.3d at 1026. Based on the Phase II study showing a trend in efficacy at 360 mg/day (120 mg tid) and significant efficacy at 720 mg/day (240 mg tid), a POSA would have reasonably expected that the lowest effective dose of DMF was between 360-720 mg/day, including at 480 mg/day (240 mg bid).

4. The Claimed Invention Would Have Been Obvious to A POSA

The claimed method of treating MS would have been obvious in view of the Phase II study alone and in combination with Nilsson and/or one of the Joshi references. FOF 48, 69. A POSA would have been motivated to consider the combined teachings of these references, because they are all directed to the use of DMF to treat MS. *Id*.

All asserted claims 1-4, 6, 8-13, and 15-16 recite the elements of: a method of treating MS with a pharmaceutical composition containing a therapeutically effective amount of 480 mg/day DMF and excipients. *Id.* 70. Dependent claims 3, 4, 9, 13, and 16 add that the DMF is administered separately in 2 equal doses. *Id.* 71. Dependent claims 8 and 10 specify that the therapeutically effective amount of DMF is administered for at least 12 weeks. *Id.* 72.

The Phase II study expressly teaches each of these elements, including dosing for over 12 weeks (an obvious approach for a chronic disease like MS), except for a dose of 480 mg/day in 2 equal doses. *Id.* 69; *see id.* 70-72. As described above, however, it would have been obvious to a

POSA to select this dose. For these reasons, the asserted claims are *prima facie* obvious.

E. If the Written Description is Sufficient, The Asserted Claims Are Anticipated

In the alternative, if the claimed invention is found described and enabled (which they are not), the equivalent disclosure of Nilsson anticipates each asserted claim. Nilsson is § 102(a) and (e) prior art. FOF 61. "A patent claim is invalid for anticipation under 35 U.S.C. § 102 when a prior art reference describes 'each and every limitation and enable[s] one of skill in the art to practice an embodiment of the claimed invention without undue experimentation." *Otonomy, Inc. v. Auris Med., AG*, 743 Fed. App'x 430, 438 (Fed. Cir. 2018). An anticipatory reference "must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). The requirements for a specification to satisfy § 112 is equivalent to that for anticipation. A "***described and enabled anticipation***" of the claimed invention is required for a "constructive reduction to practice" for § 112. *Otonomy*, 743 Fed. App'x at 434.

In the same vein as the '514 patent specification, a POSA with hindsight-knowledge of the claims can identify where each claim limitation is disclosed in Nilsson. When selectively plucked, the publication teaches all of the limitations of the claimed invention directed to: (i) a method of treating MS using DMF, (ii) at a dose of 480 mg/day (iii) administered separately in 2 equal doses, (iv) for at least 12 weeks. FOF 61, 73. But, like the '514 patent, Nilsson has the same lack of blaze marks guiding a POSA to the specific arrangement of the asserted claims. Thus, if the '514 patent specification is found to satisfy § 112, the equivalent disclosure in Nilsson did the exact same thing with an earlier priority date and should anticipate.

III. CONCLUSION

For the reasons stated herein, the Court should find the asserted claims 1-4, 6, 8-13, 15-16 of the '514 patent invalid and enter Judgment in favor of Defendants.

Dated January 31, 2020

Respectfully,

/s/ Stephen B. Brauerman

Stephen B. Brauerman (#4952)
BAYARD, P.A.
600 N. King Street, Suite 400
Wilmington, DE 19801
(302) 655-5000
sbrauerman@bayardlaw.com
Attorney for Defendants Hetero USA Inc., Hetero Labs Limited Unit-III, and Hetero Labs Limited, and Shilpa Medicare Limited

Respectfully,

/s/ John C. Phillips, Jr.

John C. Phillips, Jr. (#110)
David A. Bilson (#4986)
PHILLIPS, GOLDMAN, MCLAUGHLIN & HALL, P.A.
1200 North Broom Street
Wilmington, DE 19806-4204
(302) 655-4200
jcp@pgmhlaw.com
dab@pgmhlaw.com
Attorneys for Defendants MSN Laboratories Private Ltd. and MSN Pharmaceuticals Inc., Sandoz Inc. and Prinston Pharmaceutical Inc., and Zydus Pharmaceuticals (USA) Inc.